# Adiponectin Gene *SNP276* Variants and Central Obesity Confer Risks for Hyperglycemia in Indigenous Taiwanese

*Meng-Chuan Huang,[1,2] Tsu-Nai Wang,[3] King-Teh Lee,[4] Yu-Ju Wu,[2,5] Hung-Pin Tu,[1,2] Chih-Shan Liu,[2] Hung-Che Chiang,[1,6] and Ying-Chin Ko[1,6]*

[1]Department of Public Health, Faculty of Medicine, [2]Graduate Institute of Medicine, [3]Faculty of Public Health, Kaohsiung Medical University, [4]Departments of Surgery and [5]Nutrition and Dietetics, Kaohsiung Medical University Hospital, Kaohsiung, and [6]Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Zhunan, Taiwan.

This cross-sectional study analyzed the effects of two single nucleotide polymorphisms (SNP) of the adiponectin gene, *SNP45* and *SNP276*, on hyperglycemia in indigenous Taiwanese, and whether central obesity modulates the effects of these SNPs. Overall, 550 indigenous Taiwanese were recruited for this cross-sectional study. The subjects were categorized into a hyperglycemic group if fasting plasma glucose was >126 mg/dL ($n$=88) or the control group if fasting plasma glucose was <100 mg/dL ($n$=462). The *SNP276* TT homozygote carried greater hyperglycemia risk than *SNP276* GG [odds ratio (OR)=2.67, 95% confidence interval (CI)=1.05–6.78], but not heterozygote (OR=1.54, 95% CI=0.95–2.50). *SNP45* T>G was not associated with hyperglycemia risk. In multivariate-adjusted modeling, we found a significant relationship between *SNP276* T carriers (GT+TT) (OR=2.06, 95% CI=1.10–3.88) and central obesity (OR=4.50, 95% CI=1.91–10.61) with hyperglycemia. Compared with non-central-obese carriers of *SNP276* GG, non-central-obese *SNP276* T carriers, and central obese subjects with *SNP276* GG and *SNP276* T carriers had 5.50, 8.31 and 13.76-fold, respectively, higher risks for hyperglycemia; obese carriers of the T-containing variants experienced a combined risk for hyperglycemia. Furthermore, the hyperglycemic risks were more pronounced in leaner (non-central-obese) individuals carrying the T variant than the central-obese individuals. The adiponectin *SNP276* T variant and central obesity had independent and additive effects on hyperglycemia risks. These findings may provide valuable information regarding preventive strategies that might be useful to prevent or treat diabetes and its related complications.

**Key Words:** adiponectin, adiponectin *SNP276*, central obesity, hyperglycemia, indigenous Taiwanese
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The gene *APM1*, also known as *GBP28* or *AdipoQ*, encodes adiponectin, a protein that is exclusively expressed in adipose tissue [1]. *APM1* is located on chromosome 3q27 [2], where recent studies using genome-scans have located a susceptibility locus for type 2 diabetes and for several traits of the metabolic syndrome [3,4]. Furthermore, recent mutation screenings have detected 13 single nucleotide polymorphisms (SNPs) of the *APM1* gene in Japanese and

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Address correspondence and reprint requests to: Professor Ying-Chin Ko, Department of Public Health, Faculty of Medicine, Kaohsiung Medical University, 100 Shi-Chuan 1st Road, Kaohsiung 807, Taiwan.
E-mail: ycko@kmu.edu.tw

French populations [5,6]. Among these 13 SNPs, two [a silent T to G substitution in exon 2 (+45 T>G) and a G to T substitution in intron 2 (+276 G>T)] are commonly associated with type 2 diabetes or insulin resistance in Asians [5] and in Caucasians in France and Italy [6,7].

Weyer et al found a stronger association between decreases in adiponectin levels and obesity in people with type 2 diabetes than in healthy subjects [8]. In a genetic mouse model of obesity and lipoatrophy to explore the possible mechanisms underlying the association between decreased levels of adiponectin and insulin resistance, the administration of recombinant adiponectin in diabetic mice ameliorated insulin sensitivity by reducing triglyceride levels in muscle and liver through an increase in fatty acid β-oxidation [9,10]. The findings of these studies strongly suggest that adiponectin plays a role in the pathogenesis of insulin resistance and type 2 diabetes. In addition, there is a greater likelihood that insulin resistance and endothelial dysfunction will progress to type 2 diabetes and atherosclerosis in people with central obesity [11]. While a relationship between adiponectin and obesity seems clear, the overall effects of this relationship are unknown.

The risk of developing hyperglycemia or diabetes parallels the steadily increasing rates of obesity [12]. People of Polynesian origin are considered to express a "thrifty" genotype, a term originally hypothesized by Neel [13]. The thrifty genotype is an evolutionary development in energy storage metabolism, causing conservation of energy during food deprivation and efficient fat accumulation in response to abundant food supply. This phenomenon partially explains the higher prevalence of obesity in many Polynesian communities, including native Hawaiians [14], indigenous Maori and other Pacific Islanders in New Zealand [15] and other Pacific Islanders [16], relative to other ethnicities. Although, to Westerners, indigenous Taiwanese may look similar to other Asians, they are genetically different from Han Chinese, and recent mitochondria DNA analysis links indigenous Taiwanese with Polynesians [17]. According to the 1993–1996 National Nutrition Survey in Taiwan administered by the Department of Health, adult indigenous men and women (36.3% and 31.0%, respectively) have a higher prevalence of abdominal obesity based on the waist-to-hip ratio than the rest of the population, who are mostly of Han Chinese origin (14.1–25.5% and 8.1–21.5%, respectively) [18].

We have previously investigated the associations between some genetic variations and the extent of obesity in this indigenous community [19,20]. To the best of our knowledge, no study has compared the relative contribution of *SNP45* and *SNP276* in the context of central obesity on glycemic status in Taiwan or in other Polynesian indigenous groups. Therefore, this study investigated the relative influence of two genetic variants at the adiponectin locus (+45 T>G and +276 G>T) on glycemic status in indigenous Taiwanese and the possible role of central obesity on the impact of these SNPs on hyperglycemia in this population.

## Methods

### *Study population*

This study was a population-based epidemiological survey in an indigenous community living in Majia Township, Pingtung County, in Southern Taiwan. Majia Township consists of six villages. The area and population of this township is approximately 78 $m^2$ and 6,400 people, respectively. Ninety-five percent of the people living in this township are aborigines [21]. We performed community health examinations between August 2003 and February 2004. A total of 749 subjects were recruited in this study.

To reduce genetic variability, we included subjects whose parents were from the same tribe (2 tribes). After excluding non-indigenous and indigenous Taiwanese with more than one lineage, we were left with a total of 616 unrelated subjects for this cross-sectional study. Based on the classification of the American Diabetes Association [22], we categorized subjects with fasting plasma glucose (FPG) > 126 mg/dL or currently taking antidiabetic medications into a hyperglycemic group ($n$ = 88) and those with FPG < 100 mg/dL into a control group ($n$ = 462). Insulin resistance was assessed by the homeostasis model assessment of insulin resistance [HOMA-IR = insulin (μU/ml) × FPG (mmol/L)/22.5] [23]. The protocol for this study was approved by the Human Ethics Committee of Kaohsiung Medical University.

### *Anthropometric measurements and data collection*

Anthropometric measurements (weight, height, waist and hip circumference) were done by trained interviewers. Central obesity was defined as waist

circumference >90 cm in men or >80 cm in women, based on standards established by the International Diabetes Federation [24]. Trained interviewers assisted the participants as they completed a questionnaire collecting demographic information (age, education and tribal background) and lifestyle factors (drinking, betel quid chewing, smoking, and consumption of food groups related to glycemic control).

### *Metabolic parameters and genotype measurements*

Venous blood samples were drawn and stored at 4°C. The whole-blood samples were then sent to the laboratory of the Graduate Institute of Medicine at Kaohsiung Medical University. Aliquots of fresh serum were sent for routine clinical blood measurements (triglyceride, cholesterol, creatinine, uric acid and blood urea nitrogen) by an auto-analyzer (Beckman LX-20, Palo Alto, CA, USA) at the Department of Laboratory Medicine in Kaohsiung Medical University Hospital. FPG was measured using the Freestyle Blood Glucose Monitoring System (Abbott Diabetes Care, Alameda, CA, USA). Plasma adiponectin was measured by radioimmunoassay (Linco Research, St. Charles, MO, USA). DNA was extracted using a commercial kit (Puregene, Gentra Systems Inc., Minneapolis, MN, USA) and stored at –20°C until DNA genotyping. *SNP276 (rs1501299)* and *SNP45 (rs2241766)* were chosen for genotyping based on literature reviews and on the higher allele frequencies in the SNP database [25].

*SNP276* was detected by real-time polymerase chain reaction (ABI 7900; Applied Biosystems, Foster City, CA, USA). This assay is based on hybridization probes labeled with florescent dyes that allow fluorescence resonance energy transfer as two probes hybridize to adjacent sequences on the same unlabeled complementary strand. When a probe hybridizes over a sequence variant and forms a mismatch, the destabilized duplex causes a change in melting temperature from the completely complimentary duplex. SNP genotyping was then performed using a melting curve. The forward and reverse primers used for DNA amplification were 5′-TTC ATC ACA GAC CTC CTA CAC TGA-3′ and 5′-TCC TGT GTC TAG GCT TAG TTA AT-3′. The hybridization probes were 5′-FAM-AAA CTA TAT GAA GTC ATT CAT-3′ and 5′-VIC-ACT ATA ATG AAG GCA TTC AT-3′. The conditions of the TaqMan reaction were as follows: 50°C for 2 minutes, 95°C for 10 minutes and 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. We also randomly selected about 60 subjects (~10%) and repeated the genotyping for adiponectin *SNP276* using the same method. Except for one ambiguous genotype from one subject, the results of genotyping for the repeated samples were comparable with those of the first run.

*SNP45* was genotyped using polymerase chain reaction and restriction length polymorphism. The primers were 5′-TAT CAG TGT AGG AGG TCT GTG ATG-3′ and 5′-CAT CAC AGA CCT CCT ACA CTG ATA-3′. Amplification of the *SNP45* for adiponectin was done for 35 cycles of denaturation at 95°C for 30 seconds, annealing at 65°C for 2 minutes and extension at 72°C for 2 minutes. The amplified products were digested using *Sma I*, and the resulting fragments were separated by 2% agarose gel electrophoresis. Upon digestion with *Sma I*, the presence of the restriction site resulted in fragments of 220 bp and 152 bp in size, and 372 bp for the uncut allele.

### *Statistical analysis*

All statistical operations were performed using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA). We used student *t* tests or analysis of variance to analyze differences in continuous variables. For variables without normal distributions, data were log-transformed before testing. The distribution of categorical variables and genotypes were analyzed by $\chi^2$ tests or with Fischer's exact test for variables with $n<5$. A goodness-of-fit $\chi^2$ test was used to test the Hardy-Weinberg equilibrium comparing the observed number of subjects for each genotype with the number expected. Linear regression was used to test the linear trend of metabolic traits across different glycemic states or genotypes. A multiple logistic regression model was used to obtain adjusted odds ratios (OR) and the 95% confidence intervals (CI). Differences were considered significant when $p<0.05$ or when the 95% CI did not include 1.

## RESULTS

### *Demographic and metabolic characteristics of subjects*

Clinical characteristics of control and hyperglycemia groups are presented in Table 1. There were no significant differences between the two groups in terms

**Table 1.** Clinical characteristics of hyperglycemic and control subjects*

| | Control group ($n=462$) | Hyperglycemia group ($n=88$) | $p^{\dagger}$ |
|---|---|---|---|
| Age (yr) | 61.9 ± 13.2 | 64.0 ± 10.6 | 0.146 |
| Weight (kg) | 61.6 ± 13.2 | 65.1 ± 15.5 | 0.027 |
| Body mass index (kg/m$^2$) | 27.3 ± 8.0 | 28.5 ± 5.2 | 0.157 |
| Waist (cm) | 84.9 ± 12.3 | 90.8 ± 11.1 | < 0.001 |
| Adiponectin (μg/mL) | 9.7 ± 9.1 | 7.8 ± 6.0 | 0.088 |
| Plasma glucose (mg/dL) | 87.7 ± 8.3 | 147.0 ± 53.9 | < 0.001 |
| Insulin (μU/mL) | 3.6 ± 5.5 | 6.3 ± 7.0 | < 0.001 |
| HOMA-IR | 0.8 ± 1.1 | 2.2 ± 2.8 | < 0.001 |
| Cholesterol (mg/dL) | 181.8 ± 36.6 | 184.0 ± 38.9 | 0.609 |
| Triglyceride (mg/dL) | 126.5 ± 114.2 | 158.3 ± 147.8 | 0.024 |
| Uric acid (mg/dL) | 6.9 ± 2.0 | 7.2 ± 2.1 | 0.201 |

*Data presented as mean ± standard deviation; $^{\dagger}t$ test. HOMA-IR = Homeostasis model assessment of insulin resistance.

**Table 2.** Genotype and allele distribution for *SNP276* G > T and *SNP45* T > G in the adiponectin gene in hyperglycemic and control subjects ($n=550$)*

| | Control group ($n=462$) | Hyperglycemia group ($n=88$) | Unadjusted OR (95% CI) | $p$ | HWE$^{\dagger}$ |
|---|---|---|---|---|---|
| *SNP276* | | | | | |
| GG | 298 (64.5) | 46 (52.3) | 1 | | 0.830/0.924 |
| GT | 147 (31.9) | 35 (39.8) | 1.54 (0.95–2.50) | 0.078 | |
| TT | 17 (3.7) | 7 (7.9) | 2.67 (1.05–6.78) | 0.039 | |
| G allele | 743 (80.4) | 127 (72.7) | 1 | | |
| T allele | 181 (19.6) | 49 (27.8) | 1.59 (1.10–2.29) | 0.014 | |
| *SNP45* | | | | | |
| TT | 193 (41.8) | 43 (48.9) | 1 | | 0.814/0.304 |
| TG | 213 (46.1) | 34 (38.6) | 0.72 (0.44–1.17) | 0.182 | |
| GG | 56 (12.1) | 11 (12.5) | 0.88 (0.43–1.82) | 0.734 | |
| T allele | 599 (64.8) | 120 (68.2) | 1 | | |
| G allele | 325 (35.2) | 56 (31.8) | 0.86 (0.61–1.21) | 0.860 | |

*Data are expressed as *n* (%) or odds ratio (95% confidence interval); $^{\dagger}$control group/hyperglycemia group. OR = Odds ratio; CI = confidence interval; HWE = Hardy-Weinberg equilibrium; SNP = single nucleotide polymorphism.

of sex (males, 36.1% *vs*. 39.8%), tribal distribution (Paiwan, 89.3% *vs*. 87.5%) or education level (below junior high school, 89.0% *vs*. 94.3%). The hyperglycemic group of indigenous Taiwanese had significantly higher weight, FPG, insulin, HOMA-IR and plasma triglyceride levels than the control subjects ($p<0.05$). There were no significant differences between the two groups in terms of tobacco, alcohol or betel quid use or the consumption of carbohydrate-containing food groups such as cereals, fruits, vegetables and sweetened drinks (data not shown).

## *Associations between adiponectin SNPs and FPG*

We compared the presence of *SNP276* and *SNP45* in the adiponectin gene with glycemic status (Table 2), and found that those with the *SNP276* TT homozygote were at significantly greater risk of hyperglycemia than those with the wild type *SNP276* GG (OR = 2.67, 95% CI = 1.05–6.78; $p=0.039$). Similarly, those carrying *SNP276* T variant also had greater risk of hyperglycemia than those carrying the G variant (OR = 1.59, 95% CI = 1.10–2.29; $p=0.014$). There was no association between *SNP45* T > G and hyperglycemia. We found that the *SNP276* G > T and *SNP45* T > G polymorphisms were in Hardy-Weinberg equilibrium (Table 2).

We further compared the clinical characteristics of the subjects carrying the adiponectin *SNP276* genotype (Table 3). For the *SNP276* genotypes, body weight ($p$ for trend = 0.039), adiponectin ($p$ for trend = 0.017) and FPG ($p$ for trend = 0.001) were positively correlated with the *SNP276* T variant, and HOMA-IR was marginally correlated ($p$ for trend = 0.056). Adiponectin ($p$ for trend = 0.017) was inversely correlated

**Table 3.** Clinical characteristics of the subjects according to *SNP276* G>T and *SNP45* T>G variants of the adiponectin gene ($n$=550)*

| | *SNP276* G>T | | | $p^{\dagger}$ |
|---|---|---|---|---|
| | GG | GT | TT | |
| Age (yr) | 62.4±12.8 | 61.8±13.0 | 63.0±12.4 | 0.867 |
| Weight (kg) | 61.3±13.9 | 63.4±12.9 | 65.6±14.5 | 0.039 |
| Body mass index (kg/m$^2$) | 27.4±9.0 | 27.5±4.7 | 27.4±4.6 | 0.919 |
| Waist (cm) | 85.3±12.8 | 86.8±11.4 | 86.9±10.8 | 0.183 |
| Adiponectin (μg/dL) | 9.8±8.5 | 8.8±9.0 | 6.1±4.5 | 0.017 |
| Plasma glucose (mg/dL) | 90.5±28.4 | 94.8±35.9 | 115.3±53.1 | 0.001 |
| Insulin (μU/mL) | 4.1±6.7 | 4.1±4.0 | 3.5±3.5 | 0.139 |
| HOMA-IR | 1.0±1.9 | 1.0±0.9 | 1.2±1.7 | 0.056 |
| Cholesterol (mg/dL) | 182.3±37.4 | 181.5±35.7 | 184.2±40.3 | 0.986 |
| Triglyceride (mg/dL) | 136.3±134.8 | 119.4±71.4 | 157.1±185.7 | 0.917 |
| Uric acid (mg/dL) | 7.0±2.0 | 7.1±1.9 | 6.4±2.1 | 0.417 |

*Data presented as mean±standard deviation; †simple linear regression ($p$ for trend) was used to determine the profiles of the clinical characteristics among the different adiponectin *SNP276* G>T genotypes. HOMA-IR=Homeostasis model assessment of insulin resistance; SNP=single nucleotide polymorphism.

with the T variant. The three genotypes at *SNP45* T>G had similar metabolic traits. On examination of the association between the biochemical parameters and the *SNP276* G>T genotypes within the control or hyperglycemia subjects, there were no significant correlations between clinical parameters and the adiponectin *SNP276* GG, GT or TT genotypes in either the control or hyperglycemic subjects.

### *Relationship between adiponectin SNP276 genotypes and/or central obesity and FPG*

Multivariate logistic regression analysis was used to analyze the relationship between *SNP276* and/or central obesity with hyperglycemia. After controlling for age, sex, tribe, plasma adiponectin, serum triglyceride, stroke, heart disease, gout, and HOMA-IR, we found that the adiponectin *SNP276* T-containing genotypes (GT+TT) (OR=2.06, 95% CI=1.10–3.88) and central obesity (OR=4.50, 95% CI=1.91–10.61) were significantly associated with hyperglycemic status in this indigenous population. We further investigated the independent and joint effects of the *SNP276* T containing genotypes and central obesity on hyperglycemic status (Table 4). Compared with non-central-obese carriers of *SNP276* GG, non-central-obese subjects with *SNP276* (GT or TT), and central-obese subjects with *SNP276* GG or with *SNP276* (GT or TT) respectively, had a 5.50 (95% CI=1.17–25.85), 8.31 (95% CI=2.23–31.14) and 13.76-fold (95% CI=3.53–53.63), respectively, greater risk of hyperglycemia. Obese carriers of the T-containing variant of *SNP276* were found to be at additive risk for hyperglycemia. Furthermore, the effect of the *SNP276* T variants on hyperglycemic status was greater in leaner (non-central-obese) subjects (5.5/1.0) than in subjects with central obesity (13.76/8.31).

## Discussion

In this study, we compared the effect of two genetic variants at the adiponectin locus (+276 G>T and +45 T>G) on glycemic status in indigenous groups in Southern Taiwan and further investigated whether central obesity might modulate the impact of these polymorphisms on hyperglycemia in this population. We found evidence that both the *SNP276* T variant of the adiponectin gene and central obesity are independent risk factors for hyperglycemia (OR=2.06 and 4.50, respectively) in this population. Leaner individuals carrying the T variant were also more likely to be hyperglycemic. Finally, we found that subjects carrying the *SNP276* T-containing genotypes (GT or TT) and who were also centrally obese had the greatest risk of being hyperglycemic (OR=13.76), suggesting that obese carriers of T-containing variants were at an additive risk of being hyperglycemic.

Other studies have also found an association between the mutant T allele and adverse glucose outcomes, as well as lipid profiles [26–30]. Filippi et al [26] found a correlation between this T allele and

**Table 4.** Adjusted odds ratios for risks of hyperglycemia according to *SNP276* G > T genotypes and central obesity by multiple logistic regression analysis ($n = 550$)*

| Variables | Hyperglycemia group | Control group | Adjusted OR (95% CI) | | |
|---|---|---|---|---|---|
| | | | Model 1 | Model 2† | Model 3‡ |
| Adiponectin *SNP276* | | | | | |
| GG | 46 (52.3) | 298 (64.5) | 1 | 1 | – |
| GT + TT | 42 (47.7) | 164 (35.5) | 1.64 (1.03–1.60) | 2.06 (1.10–3.88) | – |
| Central obesity | | | | | |
| No | 20 (22.7) | 196 (43.2) | – | 1 | – |
| Yes | 68 (77.3) | 258 (56.8) | – | 4.50 (1.91–10.61) | – |
| *SNP276* and central obesity | | | | | |
| GG + non-central obesity | 9 (10.2) | 135 (29.7) | – | – | 1 |
| (GT + TT) + non-central obesity | 11 (12.5) | 61 (13.4) | – | – | 5.50 (1.17–25.85) |
| GG + central obesity | 37 (42.0) | 156 (34.4) | – | – | 8.31 (2.22–31.14) |
| (GT + TT) + central obesity | 31 (35.3) | 102 (22.5) | – | – | 13.76 (3.53–53.63) |

*Data presented as *n* (%) or adjusted odds ratio (95% confidence interval); †model 2 was adjusted for age, sex and tribal background; ‡model 3 was adjusted for age, sex, tribal background, adiponectin, hypertriglyceridemia, homeostasis model assessment of insulin resistance, gout, stroke and heart disease. OR = Odds ratio; CI = confidence interval; SNP = single nucleotide polymorphism.

lower serum adiponectin concentrations and greater insulin resistance in Italians. In cohort studies, individuals with the T allele were more susceptible to further development to type 2 diabetes [27]. The T allele has also been associated with elevated low-density lipoprotein and reduced high-density lipoprotein [28] in Canadians and higher risk for cardiovascular diseases in Americans [29]. The current study did not find an association between *SNP45* and glycemic status, although some reports have associated *SNP45* with altered glucose metabolism [5,7]. One recent cohort study also found that glucose-intolerant subjects carrying both *SNP45* G and *SNP276* T had a 4.5-fold greater risk for developing type 2 diabetes than glucose-intolerant subjects not carrying either of these alleles [27]. Similar observations have been made in case-control studies in Germany [30] and Italy [7]. However, one study of Caucasians in France did not find an association between the two SNPs and the risk of type 2 diabetes [6]. The reason for the differences in these findings is not yet known, but might be attributable to genetic differences in the populations they studied.

Our study found that the *SNP276* mutant T allele, but not the G allele, was associated with greater risk for hyperglycemia. This study found a relationship between *SNP276*, a silent polymorphism of the adiponectin gene, and increased risk for hyperglycemia (OR = 2.06, 95% CI = 1.10–3.88). However, it is not yet clear how an intron polymorphism can alter the risk for hyperglycemia. A polymorphism need not be functionally relevant itself, though it can be in complete or near-complete linkage disequilibrium with other still undiscovered SNPs of the adiponectin gene or other genes modulating the expression of adiponectin or its biological activities. We found a significant dose-dependent relationship between the at-risk T allele and decreases in concentrations of adiponectin ($p$ for trend = 0.017) and increases in FPG ($p$ for trend = 0.001), indicating that *SNP276* in an intron of the adiponectin gene may modulate glucose homeostasis by altering the expression of the adiponectin protein. Previously, Menzaghi et al [7] reported the *SNP276* G > T to be in almost complete linkage disequilibrium with an "A" insertion in the 3'untranslated region of the adiponectin gene (SNP+ 2019). The 3' untranslated regions are generally considered important in the regulation of gene expression. It has been proposed that the + 2019 insertion may alter one of the regulatory elements of the adiponectin 3' untranslated region and subsequently affect mRNA translation or degradation [31,32]. Earlier case-control and cross-sectional studies have shown associations between reduced adiponectin levels with diabetes, obesity and cardiovascular disease [5–7]. Very recently, a large prospective study suggested that higher adiponectin

concentrations might predict lower risks for type 2 diabetes [33]. Such findings suggest that adiponectin may not only serve as a marker but also as a risk factor for diabetes.

Abdominal obesity is thought to play a role in the parallel progression of insulin resistance to type 2 diabetes and in the progression from endothelial dysfunction to atherosclerosis [11]. In addition, there have been reports of associations between *APM1* gene polymorphisms and various types of obesity in different populations [7,30]. The indigenous individuals with central obesity in this study were 4.5 times more likely to be hyperglycemic than those without central obesity (OR = 4.50, 95% CI = 1.91–10.61). We also found that leaner individuals carrying the T variant were 5.5 times more likely to be hyperglycemic than those not carrying this variant, whereas obese individuals carrying the T variant (OR = 13.76) were at only 1.65 times the risk (13.76/8.31). Filippi et al [26] also reported that only leaner individuals (body mass index $< 26.2\,kg/m^2$) carrying the *SNP276* G > T variant had significantly greater insulin resistance than those with the *SNP276* GG genotypes, while obese individuals (body mass index $\geq 26.2\,kg/m^2$) showed similar resistance to insulin, regardless of whether they were carrying the *SNP276* G > T variant or the *SNP276* GG genotype. Based on this evidence, the impact of the *SNP276* gene variants on hyperglycemia and insulin sensitivity seems to be more apparent in leaner individuals than in centrally obese individuals.

Studies from animal models and human subjects have demonstrated that adiponectin, which is abundantly expressed in adipocytes, is an insulin-sensitizing hormone that is negatively regulated by obesity [34]. Most of the metabolic effects of adiponectin are dependent on the activation of adenosine monophosphate-dependent kinase [35]. AMP-dependent kinase is a fuel-sensing enzyme [36] that mediates increased glucose uptake, reduced hepatic glucose production and increased adenosine-5′-triphosphate production. The mechanism through which plasma adiponectin levels are reduced in individuals with visceral fat is not yet fully understood, but increases in inflammatory cytokine (e.g. tumor necrosis factor-α) secretion from accumulated visceral fat seems to inhibit adiponectin production [37]. This partially explains our findings that adiponectin levels are generally decreased in obese individuals and in people with inflammatory-related diseases such as diabetes and cardiovascular diseases [3,4,8,9] Hypoadiponectinemia can be caused either by interactions between genetic variations in the adiponectin gene or by the environmental factors that cause obesity. Our findings, as well as reports by Filippi et al [26], suggest that the effect of the gene variant on the hyperglycemic state in obese individuals may be too small to be detected. It is possible that the effects of central obesity on adiponectin levels or the production of inflammatory cytokines overwhelm the effect of the adiponectin *SNP276* genetic variants on glycemic state, leading to more apparent effects of adiponectin SNP276 polymorphisms on leaner individuals.

There are several limitations in the current study. First, this study had a relatively small sample size, and the study population only included two indigenous tribes. Therefore, the results of this study may not be representative of an ordinal indigenous tribe in Taiwan. Thus a larger sample size is needed to confirm our present results. Second, the possibility of linkage disequilibrium could not be determined by assuming simple associations between one polymorphism. We have suggested possible roles of adiponectin in the development of insulin resistance or the atherogenic state based on the available evidence [9,10]. The exact mechanisms underlying the role of adiponectin *SNP276* in the development of diabetes or atherosclerosis warrants further functional experimentation.

In conclusion, we found a higher prevalence of the *SNP276* T variant of the adiponectin gene in hyperglycemic indigenous Taiwanese. In our multivariate logistic regression model, the *SNP276* T-containing genotypes and central obesity were independent risk factors for hyperglycemia, and the presence of both factors in combination increased the risk for hyperglycemia. The effects of the *SNP276* T variant on hyperglycemia are more pronounced in leaner individuals than in obese individuals, suggesting that obesity may serve as a modifiable factor for adiponectin *SNP276* in modulating the risk for hyperglycemia. Because of the worldwide epidemic of early age onset of obesity, there will probably be an increase in the contribution of adiponectin to diabetes and cardiovascular risk. In light of this likely trend, a better understanding of the relationship between adiponectin gene variants or adiponectin levels in combination of obesity may help better assess the risks for diabetes or cardiovascular disease in susceptible individuals; such knowledge may allow for prevention at an earlier age.

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# 脂締素 *SNP276* 基因多型性與中央型肥胖與台灣原住民高血糖相關性之研究

黃孟娟[1,2] 王姿乃[3] 李金德[4] 吳玉茹[2,5] 杜鴻賓[1,2] 劉志珊[2] 江宏哲[1,6] 葛應欽[1,6]

高雄醫學大學 [1]醫學系 公共衛生學科 [2]醫學研究所 [3]公共衛生學系

高雄醫學大學附設醫院 [4]外科部 [5]營養部

[6]台灣國家衛生研究院 環境衛生暨職業醫學研究組

此橫斷面研究目的為探討台灣原住民脂締素（**adiponectin**）之基因多型性，***SNP45***、***SNP276*** 與中央型肥胖與高血糖之相關性。本研究共招募 **550** 位台灣原住民。高血糖之定義為禁食血糖 **≥ 126 mg/dL**（***n* = 88**）及對照組（正常血糖）則為禁食血糖 **< 100 mg/dL**（***n* = 462**）。***SNP276*** **TT** 同型結合子者相對於 ***SNP276*** **GG** 同型結合子者有 **2.67** 倍罹患高血糖之危險性（**OR = 2.76，95% CI = 1.06–6.78**），但攜帶異型結合子者（**GT**）相對於 ***SNP276*** **GG** 同型結合子則無顯著差異（**OR = 1.54，95% CI = 0.95–2.50**）。而 ***SNP45*** **T > G** 與高血糖則無顯著相關性。利用複邏輯回歸分析發現，相較於 ***SNP276*** **GG**，攜帶 ***SNP276*** **T** 對偶基因者（**GT + TT**）有 **2.06** 倍（**OR = 2.06，95% CI = 1.10–3.88**）高血糖之危險性；而相較於無中央型肥胖體位者，中央型肥胖個案有 **4.50** 倍（**OR = 4.50，95% CI = 1.91–10.61**）高血糖之危險性。更進一步，相較於無中央型肥胖體位者且 **SNP276** 攜帶 **GG** 基因型者，無中央型肥胖且 ***SNP276*** 帶有 **T** 對偶基因者、有中央型肥胖且攜帶 ***SNP276*** **GG** 基因型者或攜帶 ***SNP276*** 含 **T** 對偶基因者罹患高血糖之危險性分別為 **5.50** 倍、**8.31** 倍與 **13.76** 倍。結果顯示，中央型肥胖與 **SNP** 帶有 **T** 對偶基因者對於罹患高血糖之危險性具有加成作用。結論，脂締素基因 **SNP276** 攜帶 **T** 對偶基因和中央型肥胖者與高血糖危險性具有獨立以及加成之相關性。此研究結果提供原住民糖尿病以及心血管疾病預防策略。

**關鍵詞：**脂締素、脂締素 **SNP276** 基因多型性、中央型肥胖、高血糖、台灣原住民

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通訊作者：葛應欽教授

高雄醫學大學醫學系公共衛生學科

高雄市三民區十全一路 **100** 號